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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 07/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,082	BRIEDEN ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-39* is/are rejected.

7)☒ Claim(s) *26-28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-29-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

New claims 26-39 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 4-29-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn all previous rejection in view of claim cancellations and applicant's arguments. Examiner has withdrawn the rejections for requirement of biological certification as applicant's representative has provided such certification and also explained that some of the specific vectors claimed can be obtained using the information provided in the specification.

Claim Objections

Claims 26-39 are objected to because of the following informalities: Claims 26-39 depict the sequence identification number improperly. The correct way to depict it is as follows "SEQ ID NO:" wherein a colon precedes the actual number. See particularly 37 CFR 1.821(d). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claims 32-39 depend from a cancelled claim, claim 25 rendering them indefinite. Correction is required.

Claim 31 and claims 32-39 which depends therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 31 recites the phrase "nucleic acid molecule comprising a Hind *III* fragment which contains nucleotide sequences which hybridize under stringent conditions" to SEQ ID NO:1. First of all it is not clear to the Examiner as to what applicants mean by "contains" in the above phrase. A better term to use would be "comprise". Next, it is also not clear to the Examiner whether said nucleic acid encodes a polypeptide with any function at all, thus rendering the claims indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide with SEQ ID NO:1 encoding an enzyme of SEQ ID NO:2 having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, does not reasonably provide enablement for any or all such polynucleotides from any source including those that are variants, mutants or functional equivalents or fragments of said polynucleotide or encoding a variant, mutant or functional equivalents or fragments of said polypeptide, or polynucleotides which simply hybridize to

either SEQ ID NO:1 or fragments of the same under stringent hybridizing conditions (without any specific functions). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 29-39 are so broad as to encompass any polynucleotide encoding a polypeptide having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, from any source including those that are variants, mutants or functional equivalents or fragments of said polynucleotide or encoding a variant, mutant or functional equivalents of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under stringent hybridizing conditions. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since polynucleotides encode amino acid sequence of a protein that determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, (i.e., specific nucleotides in the polynucleotide) if

any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which nucleotides encoding specific amino acids can be modified and as well as the nucleotides required in order to make it encode the specific replacement amino acid in the original amino acid sequence based on the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single amidohydrolase. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides which encodes a variant polypeptide as well as polynucleotides with an undefined function/activity as in the case of a nucleotide sequence that simply hybridizes under stringent conditions (claim 31). The specification is limited to teaching the use of SEQ ID NO: 1 for encoding SEQ ID NO:2 but provides no guidance with regard to the making of variants and mutants or fragments of the same or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by these claims.

While recombinant and mutagenesis techniques are known, it would be an undue burden to those skilled in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino

acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all or any polynucleotide encoding a polypeptide with amidohydrolase activity including those that are variants, mutants or functional equivalents or fragments of said polynucleotide encoding a variant, mutant or functional equivalents or fragments of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under stringent hybridizing conditions because the specification does not establish: (A) regions of the polynucleotide encoding the protein structure which may be modified without affecting activity; (B) the general tolerance of amidohydrolase encoding polynucleotides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying specific nucleotides (i.e., any amino acid residue) with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides with an enormous number of modifications in the sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides having the desired biological characteristics is unpredictable

and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous rejection, applicants have traversed the above rejection arguing based on the disclosure of the amino acid sequence of SEQ ID NO:2 and coupled with the disclosure of the assays for measuring the activity, one skilled in the art would be capable of identifying variants encompassed by the claims and that all that is required is that any variants of SEQ ID NO:2 be tested for hydrolysis activity as set forth in section 4.2. Examiner respectfully disagrees with such an argument to be persuasive to overcome the above rejection. This is because, while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the specific nucleotides encoding specific amino acids need to be changed such that a variant is created endowed with all the functional properties of SEQ ID NO:2. In addition, one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without both such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified

without effecting activity; (B) the general tolerance to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid/nucleotide residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. For all the above reasons the above rejection is maintained.

Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules lacking the structure.

The specification does not contain any disclosure of the structure of all DNA sequences that encode a polypeptide having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, including those that are variants, mutants or functional equivalents or fragments of said polynucleotide. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised

guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 31-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules lacking specific function.

The specification does not contain any disclosure of the function of all DNA sequences that simply hybridize to SEQ ID NO:1 under stringent hybridizing conditions. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different functions. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao
July 6, 2004